



Office de la Propri,t, Intellectuelle du Canada
Un organisme d'Industrie Canada

(11) **CA 2 336 004**

(13) **A1**

(40) 06.01.2000
(43) 06.01.2000

(12)

(21) 2 336 004

(51) Int. Cl. 6: **A61K 31/415**

(22) 25.06.1999

(85) 22.12.2000

(86) PCT/US99/14521

(87) WO00/00184

(30) 60/090,832 US 26.06.1998

(71) DELACK, ELAINE A.,
17317 E. Lake Goodwin
Road , STANWOOD, XX (US).

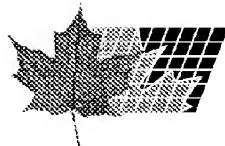
(72) DELACK, ELAINE A. (US).

(74) RUSSELL REYNEKE

(54) TRAITEMENT DE LA SCLEROSE EN PLAQUES
(54) TREATMENT FOR MULTIPLE SCLEROSIS

(57)

Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis. The histamine H2 mimicking agent is present in an amount which is effective to stimulate production of a cyclic AMP in the body. A phosphodiesterase inhibitor is used in conjunction with the histamine H2 mimicking agent to conserve the cyclic AMP which is thus produced. It is believed that the increased cyclic AMP levels serve to maintain the patient's myeline against self degeneration. The histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine. The histamine H2 mimicking agent and the phosphodiesterase inhibitor may be mixed in a gel and administered using a transdermal patch.



(21)(A1) 2,336,004

(86) 1999/06/25

(87) 2000/01/06

(72) DELACK, ELAINE A., US

(71) DELACK, ELAINE A., US

(51) Int.Cl.⁶ A61K 31/415

(30) 1998/06/26 (60/090,832) US

(54) TRAITEMENT DE LA SCLEROSE EN PLAQUES

(54) TREATMENT FOR MULTIPLE SCLEROSIS

(57) L'invention se rapporte à l'utilisation d'une substance imitant l'histamine H2 pour la fabrication d'un médicament destiné au traitement de la sclérose en plaques. Ledit agent imitant l'histamine H2 est présent en quantité suffisante pour stimuler la production par le corps d'AMP cyclique. On utilise un inhibiteur de phosphodiesterase en association avec l'agent imitant l'histamine H2 afin de conserver l'AMP cyclique ainsi produite. On pense que l'accroissement des taux d'AMP cyclique permet d'éviter l'auto-dégénérescence de la myéline du patient. Ledit agent imitant l'histamine H2 peut être du phosphate d'histamine et l'inhibiteur de phosphodiesterase peut être de la caféine. On peut mélanger l'agent imitant l'histamine H2 et l'inhibiteur de phosphodiesterase de façon à obtenir un gel que l'on administre au moyen d'un timbre transdermique.

(57) Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis. The histamine H2 mimicking agent is present in an amount which is effective to stimulate production of a cyclic AMP in the body. A phosphodiesterase inhibitor is used in conjunction with the histamine H2 mimicking agent to conserve the cyclic AMP which is thus produced. It is believed that the increased cyclic AMP levels serve to maintain the patient's myeline against self degeneration. The histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine. The histamine H2 mimicking agent and the phosphodiesterase inhibitor may be mixed in a gel and administered using a transdermal patch.



PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/00		A2	(11) International Publication Number: WO 00/00184 (43) International Publication Date: 6 January 2000 (06.01.00)
<p>(21) International Application Number: PCT/US99/14521</p> <p>(22) International Filing Date: 25 June 1999 (25.06.99)</p> <p>(30) Priority Data: 60/090,832 26 June 1998 (26.06.98) US</p> <p>(71)(72) Applicant and Inventor: DELACK, Elaine, A. [US/US]; 17317 E. Lake Goodwin Road, Stanwood, WA 98292 (US).</p> <p>(74) Agent: HATHAWAY, Todd, N.; 119 N. Commercial #620, Bellingham, WA 98225 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: TREATMENT FOR MULTIPLE SCLEROSIS</p> <p>(57) Abstract</p> <p>Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis. The histamine H2 mimicking agent is present in an amount which is effective to stimulate production of a cyclic AMP in the body. A phosphodiesterase inhibitor is used in conjunction with the histamine H2 mimicking agent to conserve the cyclic AMP which is thus produced. It is believed that the increased cyclic AMP levels serve to maintain the patient's myeline against self degeneration. The histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine. The histamine H2 mimicking agent and the phosphodiesterase inhibitor may be mixed in a gel and administered using a transdermal patch.</p>			

TREATMENT FOR MULTIPLE SCLEROSIS

BACKGROUND

5

a. Field of the Invention

The present invention relates generally to the treatment of multiple sclerosis and related disease states, and, more particularly, to medicaments for alleviating/controlling the symptoms associated with multiple sclerosis and related disease states, using compositions which induce an increased presence of cyclic AMP in the body so as to reduce or reverse demyelination of the nervous system.

b. Related Art

Multiple sclerosis (referred to from time-to-time hereinafter as "MS") is a chronic degenerative disease of the central nervous system, characterized by demyelination of the nerve axons. Symptoms include varying degrees of fatigue, numbness, tremors/muscle spasms and paralysis, coupled with a heightened susceptibility to heat and other environmental stressors. Currently, approximately 2,500,000 people worldwide have been diagnosed as having multiple sclerosis. Onset of the disease usually occurs between 20 and 40 years of age.

It is recognized that MS occurs in at least two general types, i.e., "remissive-relapsive", in which acute exacerbations are separated by periods of partial recovery, and "chronic-progressive", in which the symptoms continue generally unrelieved and there is a progressive deterioration of the patient's condition that may eventually result in total debilitation.

Efforts at treatment of MS have heretofore concentrated almost entirely on the body's autoimmune

response system. The prevailing theory has been that some agent causes the myelin sheath to be attacked by the immune system, resulting in destruction of the myelin and creation of the lesions. It is also believed that 5 certain viruses may play a role in causing or precipitating MS: In particular, the measles virus may be involved in the disease, in that studies have not only found that people suffering from MS almost invariably possess the measles antigen, but also that MS patients 10 generally have higher than normal levels of measles antibodies in their serum and cerebrospinal fluid. One theory has been that the measles or other virus triggers the T-cells to attack and destroy the myelin sheath.

Proceeding on the theory that MS is the result of an 15 autoimmune response triggered by measles or another virus, most conventional treatment techniques have involved the use of Betaseron, Avonex and/or other anti-viral substances, generally referred to collectively as "Interferon". The intended purpose of these materials is 20 to impede the RNA-DNA transcription process in the T-cells which are believed to be triggered by the virus into attacking the myelin. While interferon has demonstrated some positive results when treating remissive-relapsive type MS, it is proven almost entirely 25 ineffective against the chronic-progressive type.

Another treatment method which has yielded a limited degree of success involves the injection of adenosine monophosphate. This material is not readily absorbed, in part because it is ordinarily available only in an oil-based solution, and is not "friendly" to the patient's 30 tissues. The tissues have a tendency to wall off the material and form a small abscess capsule around it, and with each injection the material becomes harder and harder to absorb. In order for the material to be 35 absorbed, most patients must walk vigorously on a treadmill for 20-30 minutes or engage in other strenuous exercise, or else the material will simply remain at the injection site with the result that the patient becomes

extremely sore and the symptoms do not improve. Most people suffering from MS, however, are not mobile and are simply incapable of engaging in such exercise. Consequently, while many individuals experience significant benefits at the beginning of adenosine monophosphate treatments, these results eventually fade as the person's body becomes unable to absorb the material.

As will be described in greater detail below, the present invention is not postulated on conventional autoimmune theories, and instead employs application of histamine phosphate or other histamine H2 analogue to prevent/repair self-degeneration of the myelin. With the exception of experimental studies by Hinton D. Jonez, M.D. (Jonez, "Management of Multiple Sclerosis", *Postgraduate Medicine*, May 1952) and certain methods described in patents to John McMichael (U.S. 4,521,405 and 4,705,685), histamine phosphate (which is most commonly employed for diagnosis of stomach conditions) has not been used in connection with multiple sclerosis and related disorders.

The work of both Jonez and McMichael is founded on conventional autoimmune response theories. Dr. Jonez's experiments in the early 1950's attempted to manipulate the body's allergic responses using histamine phosphate, and also used the material as a vasodilator to get more blood to the brain and other parts of the nervous system. In this context, it should be understood that the present invention employs histamine phosphate to mimic histamine H2, the functions of which are confined mainly to the central nervous system, whereas the primary agent in allergic reactions is in fact histamine H1. At the time of Dr. Jonez's work, however, this distinction (between histamine H1 and histamine H2) was not fully appreciated.

McMichael's method involves the injection of a small amount of an "immunogen" consisting of viral fragments or other antigens (under the theory known as "provocative neutralization"), together with a small amount of

histamine phosphate. McMichael identifies histamine phosphate as a vasodilator, and theorizes that the histamine phosphate reacts with the immunogen to form an "active complex" which affects absorption of the material. In any event, the amounts of histamine phosphate which are involved in McMichael's treatment are far too small to have any significant impact on overall levels of histamine H2 in the body.

Accordingly, there exists a need for a treatment method which effectively alleviates the symptoms of multiple sclerosis and related disease conditions. Furthermore, there exists a need for such a method which provides an effective treatment for both the remissive-relapsive and chronic-progressive forms of the disease. Still further, there exists a need for such a method in which the treatment compositions are readily absorbed into the patient's body, without requiring resort to physical exercise for effective absorption. Still further, there exists a need for such a method which is sufficiently economical to be widely available to the great number of individuals who suffer from MS and related diseases.

SUMMARY OF THE INVENTION

The present invention has solved the problems cited above. A histamine H₂ mimicking substance is used for the manufacture of a medicament for the treatment of multiple sclerosis, the histamine H₂ mimicking substance being present in a quantity sufficient so that when the medicament is administered it is effective to stimulate production of cyclic AMP at a level which adequate to maintain myelin against self-degeneration. The histamine H₂ mimicking substance may comprise histamine phosphate, or may comprise a beta adrenergic agent such as isoproterenol.

The histamine H₂ mimicking substance may be used in combination with a phosphodiesterase inhibitor in the manufacture of the medicament. The phosphodiesterase inhibitor may comprise a methylxanthine agent. The methylxanthine agent may comprise caffeine, or may comprise theophylline or a theophylline derivative.

The medicament may be manufactured with the preferred histamine phosphate component to be taken intravenously, subcutaneously or transdermally, and with the preferred caffeine component to be taken orally or transdermally.

The present invention also provides a combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis, comprising a histamine H₂ mimicking agent and a phosphodiesterase inhibitor, the histamine H₂ mimicking agent being present in a quantity sufficient so that when the medicament is administered it is effective to stimulate production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration. Again, the histamine H₂ mimicking substance may comprise histamine phosphate or a beta adrenergic agent such as isoproterenol, and the phosphodiesterase inhibitor may comprise a methylxanthine agent such as caffeine or theophylline or a theophylline derivative.

DETAILED DESCRIPTION

The present invention provides a method for treatment of MS and related disease states by application of a histamine H₂ mimicking agent in combination with a phosphodiesterase inhibitor. A preferred histamine H₂ mimicking agent is histamine phosphate, and a preferred phosphodiesterase inhibitor is caffeine. As will be described below, the method has been observed to alleviate the symptoms of multiple sclerosis in a test application.

While not intended to be binding with respect to the practice or scope of the present invention, a hypothesis has been developed which explains the success which has been achieved with the treatment described herein. As was noted above, the conventional theory has been that demyelination is the result of an autoimmune response. However, it is also known that integrity of the nervous system is highly dependent on cyclic AMP, in that cyclic AMP stimulates the synthesis of myelin components by oligodendrocytes and Schwann cells. Studies have shown that oligodendrocytes will undergo self-induced degeneration in the absence of cyclic AMP, resulting in demyelination, but that the degenerating cells will again become viable and capable of synthesizing myelin if treated with cyclic AMP (e.g., see Kim, S. U., *Neurobiology of human oligodendrocytes in culture, Journal of Neuroscience Research 27* (1990, December)).

Cyclic AMP, in turn, is produced naturally in brain tissue, largely in the pineal gland. In persons suffering from MS, especially in the chronic-progressive phase, the levels of histamine H₂ have been observed to be very low, and the pineal gland functions tend to be atrophied. It is also known that production of cyclic AMP by the pineal gland is controlled to a large extent by the presence of histamine H₂ in the blood stream. Histamine H₂ (as differentiated from histamine H₁) is produced by cells in the central nervous system,

particularly those in the hypothalamus. In other words, certain cells in the central nervous system produce the histamine H2 which stimulates the pineal gland to produce cyclic AMP, which in turn is essential to protect the 5 myelin against self-degeneration.

It is Applicant's hypothesis that in persons suffering from MS and related disease states, the histamine H2 producing cells in the central nervous system are damaged by an agent, possibly one or more 10 strains of the measles virus, so that over time these cells cease production of histamine H2. Inadequate production of histamine H2, in turn, results in greatly reduced output of cyclic AMP from the pineal gland, leading ultimately to self-degeneration of the myelin. 15 Hence, under Applicant's hypothesis, the lesions do not result directly from an autoimmune attack on the myelin, but are instead the result of self-degeneration of the myelin precipitated by damage to the histamine H2 producing cells of the central nervous system.

20 It is further hypothesized that the damage is progressive, in that the remissive-relapsive form of the disease represents an earlier phase in which the histamine H2 cells are subjected to ongoing attack but some capacity to produce histamine H2 remains, while the 25 chronic-progressive form represents a subsequent phase in which virtually no viable histamine H2 producing cells are left.

Applicant's hypothesis is consistent with prior 30 observations concerning attempted treatment of the disease. For example, as was noted above, MS symptoms tend to respond favorably to treatment with interferon and other anti-viral agents when the disease in the remissive-relapsive phase, but such treatments become 35 ineffective when the disease enters the chronic-progressive phase. This pattern is consistent with the above hypothesis, since the interferon serves to inhibit virus replication in virus-infected cells and therefore slows damage to the remaining histamine H2 producing

cells during the remissive-relapsive phase, but when the disease has reached the chronic-progressive phase virtually all of the histamine H2 producing cells have been destroyed, so that further interferon treatments can 5 have no effect on histamine H2 output.

Additional corroborating evidence includes observations that the histamine H2 levels of MS patients in the remissive-relapsive phase tend to fluctuate, sometimes being abnormally high and at other times being 10 abnormally low. This observation is also consistent with the above hypothesis, in that it will be understood that as viruses replicate and spread they cause physical disruption of cellular structures, i.e., the cells become filled with replicated virus and ultimately "explode", 15 releasing their contents into the blood stream. In the case of histamine H2 producing cells, these contents would include not only replicated virus bodies, but also the histamine H2 contained in the cell, which accounts for the sometimes increased levels of histamine H2 which 20 are observed during periods of exacerbation in the remissive-relapsive phase.

Furthermore, histamine H2 is a known heat stress modulator, and inability to handle heat stress (reflecting a low level of histamine H2) is a classic 25 symptom of MS. Histamine H2 is also believed to regulate the number of T-cells in the body, and research has shown that people with MS tend to have abnormally low numbers of T-cells during periods of exacerbation.

Under Applicant's hypothesis, therefore, it is 30 believed that MS is precipitated by the body's inability to produce adequate levels of histamine H2. Consequently, the present invention employs histamine phosphate or selected beta adrenergic agents to replace or "mimic" the histamine H2, in an amount which is 35 sufficient to induce increased production of cyclic AMP (i.e., by the pineal gland), at levels which are adequate to eliminate and/or repair the self-degeneration of the myelin. The purpose of the caffeine or other

5 phosphodiesterase inhibitor, in turn, is to reduce the action of phosphodiesterase (the enzyme in the human body which breaks down cyclic AMP), thereby providing higher cyclic AMP levels over longer periods time without having to rely on excessively high dosages of histamine phosphate.

10 Histamine phosphate is generally preferred for the histamine H2 analogue component in the present invention, because of its wide availability and comparatively low cost, and because it very effectively mimics the action 15 of the body's natural histamine H2 (e.g., see Fact and Comparisons (January 1988)). Moreover, in addition to stimulating production of cyclic AMP, the histamine phosphate helps to provide stress modulation, again similar to the natural histamine H2.

20 Histamine phosphate is most commonly supplied in the form of histamine diphosphate. A suitable source of histamine phosphate for use in the present invention is a solution available from Eli Lilly and Company as "histamine phosphate injection, U.S.P.>"; this material is currently recognized by the US Food and Drug 25 Administration (FDA) for use as a gastric acid test. Other suitable compounds which mimic the presence of histamine H2 for purposes of stimulating cyclic AMP 30 production by the pineal gland may be used in the method of the present invention, in combination with or in place of the histamine phosphate. For example, isoproterenol and/or other beta adrenergic agents which are known or determined to be histamine H2 mimicking agents may be used in this component.

35 Similarly, caffeine is a preferred choice for the phosphodiesterase inhibitor because of its low expense and long half life, plus its minimal side effects and wider therapeutic " index. Other suitable phosphodiesterase inhibitors may also be used in accordance with the present invention to enhance the production of cyclic AMP, however, such as theophylline, theophylline derivatives, and other methylxanthine

agents. As was noted above, the purpose of this component is to enhance the effect of the increased levels of cyclic AMP which are produced by the histamine H₂ analog, by conserving the cyclic AMP against breakdown by the phosphodiesterase enzymes. In the absence of the phosphodiesterase inhibitor component, much higher levels of histamine phosphate would be required to achieve the same result, increasing the risk of adverse cardiovascular reactions and other negative side effects.

10 Caffeine citrate is generally preferred for the caffeine component in transdermal applications, due to its solubility and ability to achieve high concentrations in transdermal gel. Also, it should be noted that references to amounts and dosages of caffeine herein 15 refer to measures of caffeine base (i.e., the caffeine molecule), and do not include other materials which are sometimes found associated with the caffeine in a commercially available product.

20 The treatment composition may be administered by any suitable means, such as orally or by transdermal patch, subcutaneous injection, intravenous injection, or inhaler, to give just a few examples. Administration by transdermal patch may be preferable by many embodiments, 25 in that this provides significant advantages in terms of ease of use and consistent dosage levels. As used in this description and appended claims, the term "transdermal patch" includes both adhesive patches and other systems and devices for transdermal administration of treatment compositions.

30 The following illustrative examples relate to actual practice of the invention described above in the alleviation of the symptoms of MS patients.

Example One

5 A 39 year old, 144 pound female patient
clinically diagnosed as suffering from multiple
sclerosis was treated in accordance with the method
of the present invention. The patient has suffered
10 from Multiple Sclerosis for approximately 12 years
prior to treatment, and exhibited symptoms
indicating that the disease had advanced to the
chronic-progressive phase. Approximately 0.069
15 milligrams of histamine phosphate solution (Eli
Lily & Co., see above) were administered
subcutaneously three times daily, accompanied by
simultaneous oral administration of approximately
200 milligrams of caffeine in aqueous solution.
Clinically significant improvements were observed
within 24 hours, and full mobility was regained in
about 2 days. The patient subsequently continued
20 the treatment regimen, with no additional
exacerbation episodes having occurred to date.

Example Two

25 Ten patients participating in clinical trials
were treated in accordance with the present
invention. The patients were selected from a larger
group of candidates on the following basis:

30 (a) Each was clinically diagnosed as
suffering from multiple sclerosis;

35 (b) Each was diagnosed as being in the
"chronic-progressive" phase of the disease, so
as to minimize the possibility of erroneous
results due to spontaneous remission; and

30 (c) Each was assessed as exhibiting
physical deterioration in the range from about
5.0 to 7.5 on the MS Expanded Disability Status

5 Scale (EDSS), so that the disability would be severe enough that an improvement in condition would be clinically noticeable, but not so severe that the muscular structure would have atrophied to the point where no improvement could be observed even if neurological damage was reversed.

10 Transdermal patches were used to administer the treatment compositions, as opposed to the subcutaneous/oral regimen described in Example One. Each patch was used for an 8-hour period and contained approximately 1.1 mg of histamine diphosphate and 100 mg of caffeine citrate, 15 dissolved in approximately 0.2 ml of transdermal gel. The gel was deposited on the patch in an area approximately 6 mm in diameter, so as to minimize the area of potential skin irritation. The patch was both air and light occlusive in order to protect 20 the treatment material from decomposition.

25 Each patient's condition was assessed at the commencement of the trial to establish a baseline score. The assessments were performed using the following standard tools: (1) MS-Related Symptoms checklist (MS-RS), (2) Fatigue Severity Scale (FSS), (3) Kurtzke Functional Systems tool (FS), and (4) the EDSS scale. The assessment was repeated after forty-five (45) days of treatment, and again at the ninety (90) day point.

30 The assessment tools listed above will be familiar to those skilled in the relevant art. For purposes of illustration, however, each will be summarized below, together with representative data produced during the trial.

35 The MS-RS tool is a self-reporting system which utilizes a 6-point Likert scale (0=never, 5=always) that measures the prevalence of symptoms involving the following: fine and gross motor (arm and leg

5 The FSS tool provides a quantitative measure of fatigue, which is a prominent complaint of MS patients. The FSS tool employs a 1 to 7 Likert scale (1=strongly disagree, 7=strongly agree), and is also a self-reporting system. An example FSS report, for the same patient as in the previous example, is set forth below:

10

MS STUDY

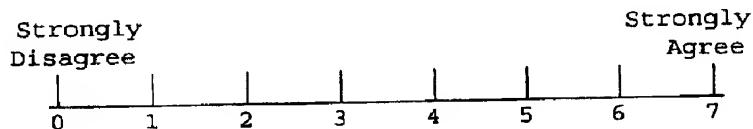
15

Respondent No: 4337
FSS (Self-reporting)

15

Please indicate to what extent you agree or disagree with the following statements using the scale:

20



25

30

35

40

45

50

		<u>Baseline</u>	<u>45 days</u>	<u>90 days</u>
1.	My motivation is lower when I am fatigued	7	5	5
2.	Exercise brings on my fatigue	5	4	5
3.	I am easily fatigued	6	5	1
4.	Fatigue interferes with my physical functioning	6	5	1
5.	Fatigue causes frequent problems for me	6	3	1
6.	My fatigue prevents sustained physical functioning	5	3	2
7.	Fatigue interferes with carrying out certain duties and responsibilities	6	2	1
8.	Fatigue is among my three most disabling symptoms	4	4	3
9.	Fatigue interferes with my work, family, or social life	3	2	1

The FSS tool provides an objective measurement of neurological impairment in the following systems: pyramidal, cerebellar, brain stem, sensory, bowel/bladder, optic, mental. The data is physician-reported, as opposed to the self-reporting systems used in the MS-RS and FSS tools. The

WO 00/00184

PCT/US99/14521

15

cumulative FS data for the trial is set forth in the following table:

CUMULATIVE TEST DATA

Functional Systems (FS)

Patient

1. 4344

Baseline	2	5	0	1	0	0	3	0
45 days	2	5	0	1	0	0	3	0
90 days	2	5	0	1	0	0	3	0

2. 4337

Baseline	3	2	3	1	0	2	1	0
45 days	3	2	3	1	0	2	1	0
90 days	1	1	1	0	0	1	1	0

3. 4366

Baseline	2	2	0	0	3	1	0	0
45 days	2	2	0	0	3	1	0	0
90 days	1	2	0	0	2-3	1	0	0

4. 4339

Baseline	3	1	2	0	2	2	2	0
45 days	3	1	2	0	2	2	2	0
90 days	3	1	2	0	2	2	2	0

5. 4336

Baseline	4	3	1	2	6	3	0	0
45 days	2	2	1	2	6	3	0	0
90 days	2	2	1	2	6	3	0	0

6. 4338

Baseline	4	3	2	3	2	3	0	0
45 days	4	3	2	3	2	3	0	0
90 days	4	3	2	3	2	3	0	0

7. 4341

Baseline	3	0	0	2	1	0	0	0
45 days	3	0	0	2	1	0	0	0
90 days	3	0	0	2	1	0	0	0

8. 4424

Baseline	4	0	0	0	2	3	0	0
45 days	4	0	0	0	2	3	0	0
90 days					INCOMPLETE			

9. 4340

Baseline	4	3	0	2	5	3	0	0
45 days	4	2	0	2	5	3	0	0
90 days	4	2	0	2	5	3	0	0

WO 00/00184

PCT/US99/14521

16

Patient	Pyramidal	Cerebellar	Brain Stem	Sensory	Bowel	Bladder	Optic	Mental	Other
10. 4550									
Baseline	2-3	0	0	1	3	0	0	0	
45 days	2-3	0	0	1	3	0	0	0	
90 days	2-3	0	0	0	3	0	0	0	

Finally, the EDSS scale measures progressive disability in increments of 0.5, where 0 represents normal and 10 indicates death due to MS. For reference, that portion of the EDSS scale which encompasses the conditions of subjects participating in the trial is reproduced below:

EXPANDED DISABILITY STATUS SCALE (EDSS)

10

Scale:

15 4.5 = Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.

20 5.0 = Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (eg, to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)

25 5.5 = Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0.)

30 6.0 = Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

35 6.5 = Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

WO 00/00184

PCT/US99/14521

17

5 7.0 Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair wheels self in standard wheelchair and transfers alone; up and about in w/c some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)

10 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)

15 Cumulative EDSS data for the trial is set forth in the following table:

Cumulative Test Data

20 **Expanded Disability Status Scale (EDSS)**

		<u>Patient</u>	<u>Baseline Score</u>	<u>45 Days Score</u>	<u>90 Days Score</u>
25	1.	4344	5.0	5.0	5.0
	2.	4337	6.0	5.5	5.0
30	3.	4366	6.0	6.0	6.0
	4.	4339	6.0	6.0	6.0
	5.	4336	6.0	5.0	5.0
35	6.	4338	6.5	6.5	6.5
	7.	4341	6.0	6.0	6.0
40	8.	4424	7.5	7.5	Inc.
	9.	4340	7.0	7.0	7.0
	10.	4550	6.0 - 6.5	6.0	6.0

45 As was noted, the full assessment was performed at the beginning of the trial and then repeated at the 45 and 90-day points. The overall results, showing the data acquired using

WO 00/00184

PCT/US99/14521

the test tools described above, are set forth in the following Table A:

TABLE A

Pl.#	MS-RS TOOL			FSS TOOL			FS TOOL			EDSS			Qualitative
	B	45 D	90D	B	45 D	90D	B	45 D	90D	B	45 D	90D	
4344	51	55.5	44	57	56	55	11	11	11	5.0	5.0	5.0	NO CHANGE
4337	67	42	19	47	31	20	12	12	5	6.0	5.5	5.0	Improved ambulation No longer using cane Increase left side strength
4366	31	7	28	45	36	33	8	8	7	6.0	6.0	6.0	Increased energy Improved ambulation Improved bladder function Reports overall improved
4339	23	33	31	46	54	48	12	12	12	6.0	6.0	6.0	NO CHANGE
4336	47	30	27	50	33	Inc	19	16	16	6.0	5.0	5.0	Increased energy Improved ambulation No longer using cane Increased sense of well being
4338	58	50	56	29	25	41	17	17	17	6.5	6.5	6.5	Reports overall improved Improved vision Improved writing function Imp. bladder function Improved balance Improved sexual function
4341	34	28	31	33	38	45	6	6	6	6.0	6.0	6.0	Increased energy Imp. sleeping at night
4424	63	53	Inc	56	63	Inc	9	9	Inc	7.5	7.5	Inc	Improved bladder function
4340	56	39	41	49	26	28	17	16	16	7.0	7.0	7.0	Decrease in ataxia Improved speech, first time able to sing in 18 years Increased energy Improved right arm function
4550	46	33	Inc	54	37	Inc	7	7	Inc	6.5	6.5	Inc	Increased energy Improved speech Imp. thought process Improved sensory function
most disabled score		least disabled score		most disabled score		least disabled score		most disabled score		least disabled score		least disabled score	
110		0		63		9		40		0		10.0	
Key: B = Baseline score		45D = 45 days on Tx score		90D = 90 days on Tx score									

5 A review of the data in Table A shows that roughly 80% of the subjects reported a qualitative improvement in their condition as a result of the treatment, and roughly 30% exhibited an improvement of one or more levels on the EDSS scale (see patient numbers 4337, 4336 and 4550). The MS-RS tool, FSS tool and FS tool, in turn, appear to show measurable improvement in about 40% of the patients (see patient numbers 4337, 4366, 4336 and 4340).

10 It should be noted that, in contrast to the general pattern of trials and studies associated with interferon treatments, the trial in Example Two recorded actual improvement in the condition of a significant number of the subjects, rather than simply a slowing in the rate of deterioration. In other words, while treatment methods based on the autoimmune theory have measured "success" in terms of slowing progression of MS, the clinical trial of the present invention demonstrated an apparent reversal of the effects of the disease.

15 Furthermore, it should be noted that the trial was conducted using essentially the smallest dose of histamine phosphate judged likely to produce observable results. Based on the study results and post-trial testing, it has been determined that an average 8-hour transdermal dose of about 1.65 mg histamine phosphate generally proves more effective. 8-hour transdermal dosages of about 2.2 mg have been tested on an individual basis, and in some instances dosages of 2.5 mg or higher may be suitable.

20 Based in part on the above examples, and using the preferred constituents of histamine phosphate and caffeine, the following approximate parameters are believed to cover the majority of dosages suitable for use with physically typical patients suffering from relatively advanced MS. It will be understood, however, that the actual dosages will vary with certain factors,

WO 00/00184

PCT/US99/14521

20

including the individual's weight, physical condition, and environmental and mental stressors, for example.

5

EXAMPLE DOSE RANGES

Caffeine:

10 Oral form
 (time release
 preferred): 600mg - 2500mg qd
 transdermal: 6-40 mg/hr

15

Histamine phosphate:

20 Intravenous: 0.01 - 2.75 mg qd-qid
 Subcutaneous
 Injection: 0.001 - 0.04 mg/kg qd-qid
 Transdermal: 0.13 - 0.63 mg/hr

25

EXAMPLE 8-HOUR TRANSDERMAL DOSE RANGES (in 0.2 m l transdermal gel)

Histamine Phosphate: 1.0 - 5.0 mg
 Caffeine (Caffeine Citrate): 50 - 300 mg

30

It is to be recognized that various alterations, modifications, and/or additions may be introduced into the constructions and arrangements of parts described above without departing from the spirit or ambit of the present invention.

91

WHAT IS CLAIMED IS:

1. Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis, the histamine H2 mimicking substance being present in a quantity sufficient so that when the medicament is administered it is effective to stimulate production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration.
10
2. Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 1, wherein the histamine H2 mimicking substance comprises histamine phosphate.
15
3. Use of a histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 1, wherein the histamine H2 mimicking substance comprises a beta adrenergic agent.
20
4. Use of histamine H2 mimicking substance for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 3, wherein the beta adrenergic agent comprises isoproterenol.
25
5. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis, the histamine H2 mimicking substance being present in a quantity sufficient so that when the medicament is administered it is effective to stimulate production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration.
30
35
6. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the

manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 5, wherein the phosphodiesterase inhibitor comprises a methylxanthine agent.

5

7. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 6, wherein the 10 methylxanthine agent comprises caffeine.

8. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple 15 sclerosis as claimed in Claim 6, wherein the methylxanthine agent comprises theophylline or a theophylline derivative.

9. Use of a histamine H2 mimicking substance in 20 combination with a phosphodiesterase inhibitor for the manufacture of a medicament for treatment of multiple sclerosis as claimed in any one of Claims 5 to 8, wherein the histamine H2 mimicking substance comprises histamine phosphate.

25

10. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in any one of Claims 5 to 8, wherein 30 the histamine H2 mimicking substance comprises a beta adrenergic agent.

11. Use of a histamine H2 mimicking substance in combination with a phosphodiesterase inhibitor for the 35 manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 10, wherein the beta adrenergic agent comprises isoproterenol.

12. Use of a histamine H₂ mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of medicament for the treatment of multiple sclerosis as claimed in Claim 9 when appendant from Claim 5 7, wherein the medicament comprises between about 600mg and 2500 mg of caffeine to be taken orally, and between about 0.01 and 2.75 mg of histamine phosphate to be taken intravenously.

10 13. Use of a histamine H₂ mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 9 when appendant from Claim 7, wherein the medicament comprises between about 600 mg and 2500 mg of caffeine to be taken orally, and between about 15 0.001 and 0.04 mg/kg of histamine phosphate to be injected subcutaneously.

20 14. Use of a histamine H₂ mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 9 when appendant from Claim 7, wherein the medicament comprises between about 600 mg and 2500 mg of caffeine to be take orally, and between 25 about 0.13 and 0.63 mg/hr of histamine phosphate to be taken transdermally.

30 15. Use of a histamine H₂ mimicking substance in combination with a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of multiple sclerosis as claimed in Claim 9 when appendant from Claim 7, wherein the medicament comprises between about 6 mg/hr and 40 mg/hr of caffeine to be taken transdermally, and between about 35 0.13 and 0.63 mg/hr histamine phosphate to be taken transdermally.

16. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment

of multiple sclerosis, comprising a histamine H₂ mimicking agent and a phosphodiesterase inhibitor, the histamine H₂ mimicking agent being present in a quantity sufficient so that when the medicament is administered it is effective to stimulate production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration.

10 17. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis as claimed in Claim 16, wherein the histamine H₂ mimicking substance comprises histamine phosphate.

15 18. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis as claimed in Claim 16, wherein the histamine H₂ mimicking substance comprises a beta adrenergic agent.

20 19. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis as claimed in Claim 16, wherein the beta adrenergic agent comprises isoproterenol.

25 20. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis as claimed in Claim 17, wherein the phosphodiesterase inhibitor comprises a methylxanthine agent.

30 21. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment of multiple sclerosis as claimed in claim 20, wherein the methylxanthine agent comprises caffeine.

35 22. A combined preparation for simultaneous, separate, or sequential use in therapy for the treatment

WO 00/00184

PCT/US99/14521

25

of multiple sclerosis as claimed in Claim 20, wherein said methylxanthine agent comprises theophylline or a theophylline derivative.

5